

## REMARKS

### *Status of the Claims*

Claims 3-6, 8-10, 14, 17, 18, and 21-36 are currently pending and stand rejected.

### *Rejection under 35 U.S.C. § 112, second paragraph*

Claims 3-6, 8-10, 14, 17-18, and 21-36 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

The Office Action asserts that the recitation of "byproduct polypeptide" is indefinite because the Examiner "cannot estimate [the] metes and bounds of the claim, since the byproduct peptide is not defined and no examples are provided in the claims." Office Action, page 2.

Applicants respectfully disagree and submit that the claims make clear that "byproduct peptide" contains an O-acetylserine residue in place of a serine. *See e.g.*, claims 9 ("a byproduct comprising an O-acetylserine residue in place of a serine residue"), 10 (same), 17 (same), 18 (same), 33 (same) and 35 (same). Applicants also note that the specification describes the "byproduct polypeptide" as containing an O-acetylserine residue in place of a serine. *See e.g.*, Specification at page 5, lines 5-10 and page 12, lines 10-11. In particular, the specification teaches that the recombinant production of hANP leads to the formation of an impurity, a byproduct polypeptide referred to as "R1." Applicants discovered that the byproduct polypeptide "R1" was a modified hANP polypeptide where serine was acetylated to produce O-acetylserine that was incorporated in place of serine during translation of hANP.<sup>1</sup> Specification at page 7, lines 1-5 and Example 2, in particular, page 16, lines 21-26; *See also* Exhibit A (showing the formula for serine and O-acetylserine). Accordingly, Applicants submit that one of skill in the art would understand the metes and bounds of the term "byproduct peptide."

In view of the foregoing, Applicants respectfully request withdrawal of this rejection.

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<sup>1</sup> Applicants submit that the terms "serine" and "O-acetylserine" are well-known terms in the art.

***Rejections under 35 U.S.C. § 102***

Claims 3-6, 8-20, 17-18, 21-31, 33, and 35 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by UK Patent Application GB 2 180 539 ("GB '539"). Applicants respectfully traverse this rejection.

The Office Action asserts that GB '539 discloses the overnight culture of *E. coli* containing an expression vector in an L-broth comprising yeast extract. Office Action at page 3. The Office Action then cites an unrelated second reference, Manual of BBL Products and Laboratory Procedures ("Manual"), to support the supposition that "yeast extract is composed of different amino acids." Office Action at 3.

Applicants' previous response pointed out that GB '539 does not describe the composition of the yeast extract, the supplier of the yeast extract, and/or what amounts of methionine, histidine, and glycine are present. See Petition for Extension of Time, Reply, and Amendment under 37 C.F.R. § 1.111 ("Response") filed on June 26, 2007 at page 9. Applicants further asserted that to the extent the Examiner is relying on inherency, neither the GB '539 nor the Manual make clear that the missing descriptive matter (*i.e.*, the amount of methionine, histidine, and glycine is present in an amount effective to reduce byproduct formation) is necessarily present in the references. *Id.*

Nonetheless, the Office Action maintains the rejection and relies on inherency stating "...L-broth contains yeast extract and thus will contain amino acids such as methionine, histidine, or glycine." Office Action at page 4.

Applicants respectfully submit that this response is insufficient to maintain the rejection. The issue is not whether the particular amino acids are present, but whether they are present in an amount effective to reduce byproduct formation as required by the claims. Applicants submit that the Manual does not teach an amount effective to reduce byproduct formation. In particular, the Manual provides an example of a yeast extract which comprises, as percentage of weight, 0.944% methionine, 1.25% histidine, and 2.83% glycine. This translates into 9.4 mg of methionine, 12.5 mg of histidine, and 28.3 mg of glycine per gram of yeast extract. While Applicants maintain that GB '539 does not describe the composition of the yeast extract or the supplier of the yeast extract, based on the information provided in the Manual, the L-broth used by GB '539 would comprise 47 mg methionine, 62.5 mg histidine, and 141.5 mg glycine per liter of medium. These amounts are insufficient to reduce the formation of byproduct polypeptide in

an amount greater than or equal to 50% as compared to a control medium with no methionine, histidine, or glycine added. *See e.g.*, Examples 2-3 of the Specification.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 3-6, 8-10, 17-18, 21-31, 33, and 35 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent Application Publication No. 2003/0170811 (September 11, 2003) Ueda, *et al.* ("the '811 publication"). Applicants respectfully traverse this rejection.

The Office Action asserts that the '811 publication discloses the overnight culture of *E. coli* containing an expression vector in L-broth. Office Action at page 4. The Office Action then cites an unrelated second reference, Handbook of Microbiological Media ("Handbook"), to support the supposition that L-broth "contains yeast extract, which is composed of different amino acids." *Id.*

Applicants' previous response pointed out that the '811 publication does not describe the composition of the L-broth, the supplier of the L-broth, and/or what amounts of methionine, histidine, and glycine may be present. *See* Response at page 10. Applicants further asserted that to the extent the Examiner is relying on inherency, neither the '811 publication nor the Handbook makes clear that the missing descriptive matter (*i.e.*, the amount of methionine, histidine, and glycine is present in an amount effective to reduce byproduct formation) is necessarily present in the references. *Id.* at pages 10-11.

Nonetheless, the Office Action maintains the rejection and responds by stating "L-broth with the yeast extract is commonly used in the art as a source of amino acids and thus the reference of Ueda *et al.* still applies." Office Action at page 4.

Applicants respectfully submit that this response is insufficient to maintain the rejection. First, the assertion that "L-broth with the yeast extract is commonly used in the art as a source of amino acids" does not address the issue of not whether the particular amino acids are present in an amount effective to reduce byproduct formation as required by the claims. Second, even assuming the composition of the yeast extract used by the '811 publication is substantially similar to that in the Manual, the amounts of methionine, histidine, and glycine would be insufficient to reduce the formation of byproduct polypeptide in an amount greater than or equal

to 50% as compared to a control medium with no methionine, histidine, or glycine added. *See e.g., Examples 2-3 of the Specification.*

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection.

***Rejection under 35 U.S.C. § 103(a)***

Claims 3-6, 8-10, 14, 17-18, and 21-36 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,670,340 (September 23, 1997) Yabuta, *et al.* ("the '340 patent"). Applicants respectfully traverse this rejection.

In Applicants prior response, Applicants explained that Yabuta does not teach each and every claim limitation. Among other things, Applicants pointed out that Yabuta does not teach the addition of methionine **and at least one of** histidine or glycine in an amount effective to reduce byproduct formation.

Nonetheless, the Office Action maintains the rejection stating that "the production of O-acetyl-serine as a byproduct would be expected as part of a cysteine metabolic pathway in [*E. coli*] during the production of a protein comprising culturing [*E. coli*] host cells...as suggested by Yabuta." Office Action at page 7.

Applicants respectfully submit that this statement is inconsistent with the teachings of the specification that indicate the nature of the impurity in recombinant hANP was unknown at the time of filing this patent application. Indeed, one novel aspect of the invention is the identification of this impurity as the formation of O-acetyl-serine. Specification at page 5, lines 5-10. Another novel aspect is the reduction of this impurity. Specification at page 5, lines 11-17. The '340 patent is silent on these aspects and therefore does not teach or suggest the claimed method.

The Office Action concludes by citing to page 17 of the specification and stating that: any one of amino acids: alanine, glycine, serine, methionine or histidine can be added to the suspension of the cell culture in the instant invention, and that Yabuta *et al.* teach[es] [the] addition of L-methionine, for example. Also, the byproduct will be reduced when compared to a medium with no methionine. Further, Yabuta *et al.* teach[es] [the] addition of 2.0 g/L of L-methionine, however, in the absence of the evidence to the contrary it will still be obvious to add 3 g/L of methionine to achieve the same goal. Office Action at pages 7-8.

As an initial matter, Applicants respectfully submit that it is improper to use the novel aspects of the invention as described in the specification to supplement a prior art rejection. Furthermore, as set forth in the specification, the nature of the byproduct peptide and its reduction were unknown prior to the filing this patent application and thus a person of ordinary skill in the art would not have been aware of the claimed method of reducing the formation of byproduct peptide. Specification at page 5, lines 5-10. The '340 patent does not establish the nexus between elevated levels of methionine and at least one of histidine or glycine to reduce byproduct peptide formation. Furthermore, the Office Action has not provided any reason that one of ordinary skill in the art would have added 3 g/L of methionine to achieve an unknown goal. Accordingly, Applicants submit that the Office Action has relied upon conclusory statements without basis to support the rejection.

Applicants respectfully request reconsideration and withdrawal of this rejection.

**CONCLUSION**

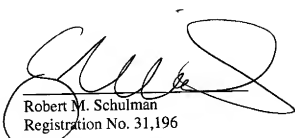
Applicants respectfully submit that claims 3-6, 8-10, 14, 17-18, and 21-36 are in condition for allowance, and such disposition is earnestly solicited. Should the Examiner believe that any patentability issues remain after consideration of this Response, the Examiner is invited to contact the Applicants' undersigned representative to discuss and resolve such issues.

In the event that a variance exists between the amount tendered and that deemed necessary by the U.S. Patent and Trademark Office to enter and consider this Response or to maintain the present application pending, please credit or charge such variance to the undersigned's **Deposit Account No. 50-0206**.

Respectfully submitted,

Dated: March 18, 2008

By:

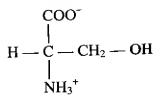


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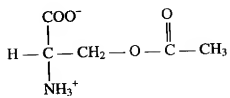
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**EXHIBIT A**



Serine



O-acetylserine